In this issue

By John Ashkenas, Science Editor

Gene therapy for arthritis

(See articles on pages 1275–1284 and 1293–1301.)

The ability of immune cells to home to peripheral lymphoid organs or target tissues is critical to autoimmune pathogenesis, but it also makes these cells a promising vehicle for delivering therapeutic agents to the relevant tissues. Two reports in this issue apply this principle to suppress collagen-induced arthritis (CIA), a mouse model of rheumatoid arthritis. Nakajima and colleagues previously used adoptive transfer of transgenic T cells to block autoimmune responses in the CNS, and here they employ a similar strategy, transducing collagen-specific helper T cells with an antagonist of the cytokine IL-12. They introduce the modified T cells into mice that would otherwise develop CIA and show that the cells home efficiently to the synovium and block inflammation in situ. In contrast, their CNS-directed T cells, which express the same immunosuppressive transgene and are effective against a different autoimmune disease, do not persist in the synovium and fail to suppress arthritis. In a complementary effort, Morita et al. show that dendritic cells (DCs), which control the proliferation and immunological properties of T cells, can also be used to deliver an appropriate regulatory protein. These authors generated DCs, transduced them with IL-4, and reintroduced them into mice. The modified DCs can interact with collagen-specific T cells and drive them toward the Th2 phenotype, which is associated with tolerance to the corresponding antigens. Here again, tissue targeting is crucial, since the DCs must reach the spleen if they are to have their desired effect on T-cell development. Morita et al. show that delivery by intraperitoneal injection leads to the most efficient targeting of DCs to the spleen and confers the greatest protection from arthritis.

The tight junction as a selective barrier

(See article on pages 1319–1327.)

Epithelial cells must be closely apposed and form tight junctions with one another if they are to maintain a different composition in the extracellular fluid at their apical and basolateral sides. Tight junctions provide a physical block to solute diffusion around cells, and freeze-fracture electron microscopic images of these structures reveal multiple parallel strands that extend along the cell surface and contact the neighboring cell. However, tight junctions do not simply provide a gasket around each cell but rather block the flow of different classes of solutes selectively and in characteristic ways in different epithelia. Here, Van Itallie et al. argue that these functional differences arise from differential expression of claudins, transmembrane proteins that localize to the tight junction. Claudin-4 is normally found in the pancreas and in certain cells of the colon, but the authors use an inducible promoter to drive expression of this protein in MDCK cells, a well studied model epithelial cell line. They find that as claudin-4 levels rise, the number of strands seen in micrographs of the tight junction increases and the paracellular flow of Na^+ ions and of other monovalent cations declines. Remarkably, however, transport of uncharged or anionic solutes is unchanged. The molecular and structural basis of this selectivity remains a puzzle.

Immune responses of at-risk but HIV-free women

(See article on pages 1303–1310.)

An ideal AIDS vaccine might be one that stimulates the cellular immune system so efficiently that, despite repeated exposure to the virus, an individual never shows signs of viremia or even seroconverts against HIV epitopes. It is still far from clear how to provide anyone this level of protection, but accumulating data from a cohort of at-risk women — sex workers in the AIDS-ravaged community of Nairobi — hint at some of the properties of an immune system that can apparently repel the virus despite ongoing exposure. Kaul et al. have followed this group for some years, and they have found that persistently seronegative women seem to be protected by a vigorous T cell–mediated response to infected cells, while those who have seroconverted eventually succumb to the disease. These authors now report on the HIV epitopes recognized by cytotoxic T lymphocytes from presymptomatic but seropositive women and from persistently seronegative women. The authors previously identified several class I MHC alleles that are associated with this protected status, suggesting a genetic basis for the difference in disease progression. Following up on this work, they now show that the protective alleles present a distinct set of HIV epitopes in the two groups of women. Those epitopes that are exclusively or preferentially recognized in persistently seronegative women could provide the basis of a vaccine that can activate T-cell responses that block progression of the disease.